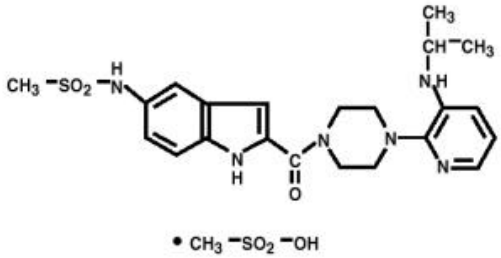
RESCRIPTOR®
brand of delavirdine mesylate tablets

WARNING: RESCRIPTOR Tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for RESCRIPTOR based on survival or incidence of AIDS-defining clinical events in a completed trial comparing RESCRIPTOR plus didanosine with didanosine monotherapy (see DESCRIPTION OF CLINICAL STUDIES).

Resistant virus emerges rapidly when RESCRIPTOR is administered as monotherapy. Therefore, RESCRIPTOR should always be administered in combination with appropriate antiretroviral therapy.

DESCRIPTION

RESCRIPTOR Tablets contain delavirdine mesylate, a synthetic non-nucleoside reverse transcriptase inhibitor of the human immunodeficiency virus type 1 (HIV-1). The chemical name of delavirdine mesylate is piperazine, 1-[3-[(1-methyl-ethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)amino]-1H-indol-2-yl]carbonyl]-, monomethanesulfonate. Its molecular formula is C22H28N6O3S • CH4O3S, and its molecularweight is 552.68. The structural formula is:



Delavirdine mesylate is an odorless white-to-tan crystalline powder. The aqueous solubility of delavirdine free base at 23 °C is 2942 μg/mL at pH 1.0, 295 μg/mL at pH 2.0, and 0.81 μg/mL at pH 7.4.

Each RESCRIPTOR Tablets, for oral administration, contains 100 or 200 mg of delavirdine mesylate (henceforth referred to as delavirdine). Inactive ingredients consist of lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and carnauba wax. In addition, the 100-mg tablet contains Opadry White YS-1-7000-E and the 200-mg tablet contains hydroxypropyl methylcellulose, Opadry White YS-1-18202-A and Pharmaceutical Ink Black.

MICROBIOLOGY

Mechanism of action: Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Delavirdine binds directly to reverse transcriptase (RT) and blocks RNA-dependent and DNA-dependent DNA polymerase activities. Delavirdine does not compete with template: primer or deoxynucleoside triphosphates. HIV-2 RT and human cellular DNA polymerases α, γ, or δ are not inhibited by delavirdine. In addition, HIV-1

group O, a group of highly divergent strains that are uncommon in North America, may not be inhibited by delavirdine.

In vitro HIV-1 susceptibility: In vitro anti–HIV-1 activity of delavirdine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV-1. IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) for laboratory isolates (N=5) ranged from 0.005 to 0.030 μM and 0.04 to 0.10 μM, respectively. Mean IC_{50} of clinical isolates (N=74) was 0.038 μM (range 0.001 to 0.69 μM); 73 of 74 clinical isolates had an $IC_{50} \leq 0.18$ μM. The IC_{90} of 24 of these clinical isolates ranged from 0.05 to 0.10 μM. In drug combination studies of delavirdine with zidovudine, didanosine, zalcitabine, lamivudine, interferon-α, and protease inhibitors, additive to synergistic anti–HIV-1 activity was observed in cell culture. The relationship between the in vitro susceptibility of HIV-1 RT inhibitors and the inhibition of HIV replication in humans has not been established.

Drug resistance: Phenotypic analyses of isolates from patients treated with delavirdine as monotherapy showed a 50-fold to 500-fold reduction in sensitivity in 14 of 15 patients by week 8 of therapy. Genotypic analyses of HIV-1 isolates from patients receiving delavirdine plus zidovudine combination therapy (N=19) showed mutations in 16 of 19 isolates by week 24 of therapy. Mutations occurred predominantly at position 103 and less frequently at positions 181 and 236. In a separate study, an average 86-fold increase in the zidovudine sensitivity of patient isolates (N=24) was observed after 24 weeks on delavirdine and zidovudine combination therapy. The clinical relevance of the phenotypic and the genotypic changes associated with delavirdine therapy has not been determined.

Cross-resistance: Rapid emergence of HIV strains that are cross-resistant to certain NNRTIs has been observed in vitro. Mutations at positions 103 and 181 have been associated with resistance to other NNRTIs. RESCRIPTOR may confer cross-resistance to other non-nucleoside reverse transcriptase inhibitors when used alone or in combination.

The potential for cross-resistance between delavirdine and protease inhibitors is low because of the different enzyme targets involved. The potential for cross-resistance between NNRTIs and nucleoside analogue RT inhibitors is low because of different sites of binding on the viral RT and distinct mechanisms of action.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption and Bioavailability: Delavirdine is rapidly absorbed following oral administration, with peak plasma concentrations occurring at approximately one hour. Following administration of delavirdine 400 mg tid (n=67, HIV-1–infected patients), the mean ± SD steady-state peak plasma concentration (C_{max}) was 35 ± 20 μM (range 2 to 100 μM), systemic exposure (AUC) was 180 ± 100 μM • hr (range 5 to 515 μM • hr) and trough concentration (C_{min}) was 15 ± 10 μM (range 0.1 to 45 μM). The single-dose bioavailability of delavirdine tablets relative to an oral solution was 85 ± 25% (n=16, non-HIV–infected subjects). The single-dose bioavailability of delavirdine tablets (100 mg strength) was increased by approximately 20% when a slurry of drug was prepared by allowing delavirdine tablets to disintegrate in water before administration (n=16, non-

HIV–infected subjects). The bioavailability of the 200 mg strength delavirdine tablets has not been evaluated when administered as a slurry, because they are not readily dispersed in water (see DOSAGE AND ADMINISTRATION).

Delavirdine may be administered with or without food. Following single-dose administration of delavirdine tablets with a high-fat meal (874 kcal, 57 g fat), mean C_{max} was decreased by 60% and mean AUC was decreased by 26%, relative to fasted administration (n=12, non-HIV–infected subjects). In a multiple-dose study, delavirdine was administered every eight hours with food or every eight hours, one hour before or two hours after a meal (n=13, HIV-1–infected patients). Patients remained on their typical diet throughout the study; meal content was not standardized. When multiple doses of delavirdine were administered with food, mean C_{max} was reduced by 22% but AUC and C_{min} were not altered.

Distribution: Delavirdine is extensively bound (approximately 98%) to plasma proteins, primarily albumin. The percentage of delavirdine that is protein bound is constant over a delavirdine concentration range of 0.5 to 196 μM. In five HIV-1–infected patients whose total daily dose of delavirdine ranged from 600 to 1200 mg, cerebrospinal fluid concentrations of delavirdine averaged 0.4% ± 0.07% of the corresponding plasma delavirdine concentrations; this represents about 20% of the fraction not bound to plasma proteins. Steady-state delavirdine concentrations in saliva (n=5, HIV-1–infected patients who received delavirdine 400 mg tid) and semen (n=5 healthy volunteers who received delavirdine 300 mg tid) were about 6% and 2%, respectively, of the corresponding plasma delavirdine concentrations collected at the end of a dosing interval.

Metabolism and Elimination: Delavirdine is extensively converted to several inactive metabolites. Delavirdine is primarily metabolized by cytochrome P450 3A (CYP3A), but in vitro data suggest that delavirdine may also be metabolized by CYP2D6. The major metabolic pathways for delavirdine are N-desalkylation and pyridine hydroxylation. Delavirdine exhibits nonlinear steady-state elimination pharmacokinetics, with apparent oral clearance decreasing by about 22-fold as the total daily dose of delavirdine increases from 60 to 1200 mg/day. In a study of ^{14}C-delavirdine in six healthy volunteers who received multiple doses of delavirdine tablets 300 mg tid, approximately 44% of the radiolabeled dose was recovered in feces, and approximately 51% of the dose was excreted in urine. Less than 5% of the dose was recovered unchanged in urine. The apparent plasma half-life of delavirdine increases with dose; mean half-life following 400 mg tid is 5.8 hours, with a range of 2 to 11 hours.

In vitro and in vivo studies have shown that delavirdine reduces CYP3A activity and inhibits its own metabolism. In vitro studies have also shown that delavirdine reduces CYP2C9 and CYP2C19 activity. Inhibition of CYP3A by delavirdine is reversible within 1 week after discontinuation of drug.

Special Populations

Hepatic or Renal Impairment: The pharmacokinetics of delavirdine in patients with hepatic or renal impairment have not been investigated (see PRECAUTIONS).

Age: The pharmacokinetics of delavirdine have not been studied in patients <16 years or >65 years of age.

Gender: Following administration of delavirdine (400 mg every eight hours), median delavirdine AUC was 31% higher in female patients (n=12) than in male patients (n=55).
Race: No significant differences in the mean trough delavirdine concentrations were observed between different racial or ethnic groups.

Drug Interactions (see also PRECAUTIONS-Drug Interactions)

Antacids: In a single-dose study in twelve healthy volunteers, simultaneous administration of 300 mg delavirdine with alumina and magnesia oral suspension resulted in a 41 ± 19% reduction in delavirdine AUC (see PRECAUTIONS-Drug Interactions).
Clarithromycin: In a study in six HIV-1–infected patients, coadministration of clarithromycin (500 mg bid) with delavirdine (300 mg tid) resulted in a 44 ± 50% increase in delavirdine AUC. Compared to historical data, clarithromycin AUC was increased by approximately 100% and 14-hydroxyclarithromycin AUC was decreased by 75%.
Didanosine: In a study in nine HIV-1–infected patients, simultaneous administration of didanosine (125 mg or 250 mg bid) with delavirdine (400 mg tid) for two weeks resulted in an approximately 20% decrease in both didanosine AUC and delavirdine AUC, relative to when administration of delavirdine and didanosine was separated by at least one hour (see PRECAUTIONS-Drug Interactions).
Fluconazole: In a study in eight HIV-1–infected patients, coadministration of fluconazole (400 mg once daily) with delavirdine (300 mg tid) did not significantly alter the pharmacokinetics of delavirdine. Compared to historical data, fluconazole pharmacokinetics were not altered by delavirdine.
Fluoxetine: Population pharmacokinetic data available for 36 patients suggest that fluoxetine increases trough plasma delavirdine concentrations by about 50%.
Indinavir: Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400 mg single dose of indinavir with delavirdine (400 mg tid) resulted in indinavir AUC values slightly less than those observed following administration of an 800 mg dose of indinavir alone. Also, coadministration of a 600 mg dose of indinavir with delavirdine (400 mg tid) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800 mg dose of indinavir alone. Indinavir had no effect on delavirdine pharmacokinetics (see PRECAUTIONS-Drug Interactions).
Ketoconazole: Population pharmacokinetic data available for 26 patients suggest that ketoconazole increases trough plasma delavirdine concentrations by about 50%.
Phenytoin, Phenobarbital, and Carbamazepine: Population pharmacokinetic data available for eight patients suggest that coadministration of phenytoin, phenobarbital, or carbamazepine with delavirdine results in a substantial reduction in trough plasma delavirdine concentrations (see PRECAUTIONS-Drug Interactions).
Rifabutin: In a study in seven HIV-1–infected patients, coadministration of rifabutin (300 mg once daily) with delavirdine (400 mg tid) resulted in an 80 ± 10% decrease in delavirdine AUC. Compared to historical data, rifabutin AUC was increased by at least 100% (see PRECAUTIONS-Drug Interactions).
Rifampin: In a study in seven HIV-1–infected patients, coadministration of rifampin (600 mg once daily) with delavirdine (400 mg tid) resulted in a 96 ± 4% decrease in delavirdine AUC (see PRECAUTIONS-Drug Interactions).

Ritonavir: Preliminary data (n=13) indicate that coadministration of delavirdine (400 mg or 600 mg bid) with ritonavir (300 mg bid) did not alter ritonavir pharmacokinetics. Coadministration of ritonavir (300 mg bid) with delavirdine (400 mg bid) did not significantly alter delavirdine pharmacokinetics (n=9). The pharmacokinetic interaction between delavirdine and ritonavir at their recommended doses has not been studied (see PRECAUTIONS-Drug Interactions).

Saquinavir: In 13 healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a five-fold increase in saquinavir AUC. In seven healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a 15 ± 16% decrease in delavirdine AUC (see PRECAUTIONS-Drug Interactions).

Sulfamethoxazole and Trimethoprim/Sulfamethoxazole (TMP/SMX): Population pharmacokinetic data available for 311 patients suggest that the pharmacokinetics of delavirdine are not affected by sulfamethoxazole or TMP/SMX.

Zidovudine: Zidovudine and delavirdine do not alter one another's pharmacokinetics.

INDICATIONS AND USAGE

RESCRIPTOR Tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for RESCRIPTOR based on survival or incidence of AIDS-defining clinical events in a completed trial comparing RESCRIPTOR plus didanosine with didanosine monotherapy (see DESCRIPTION OF CLINICAL STUDIES).

Resistant virus emerges rapidly when RESCRIPTOR is administered as monotherapy. Therefore, RESCRIPTOR should always be administered in combination with appropriate antiretroviral therapy.

DESCRIPTION OF CLINICAL STUDIES

In two of the clinical studies described below (Study 0021, Part 1 and Study 0017), an experimental HIV nucleic acid amplification assay was used to estimate the level of circulating HIV RNA in plasma. In the clinical study ACTG 261, also described below, an approved HIV nucleic acid amplification assay was used.

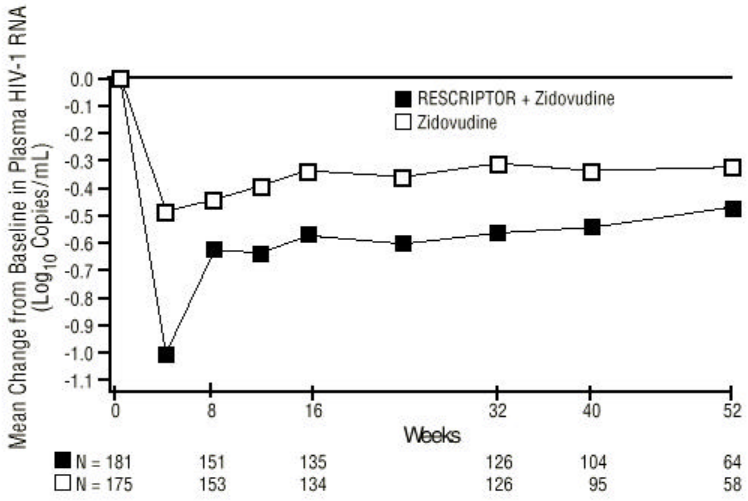
Figures 1-3 below present results for all patients with data available at the time points shown. The decrease in sample size reflects patients leaving the study, missed visits, and those who had not reached specified time points at data cutoff. In general, patients who left the study had lower CD4 cell counts and higher plasma HIV RNA values than patients remaining on study. Therefore, absolute changes from baseline are overstated in all treatment arms, increasingly so at later time points. However, the added effect of delavirdine treatment relative to the control arms does not appear to be significantly affected by patient dropout.

Study 0021, Part 1: RESCRIPTOR-Zidovudine Dual Therapy Trial

Study 0021, Part 1 was a randomized, double-blind trial comparing treatment with RESCRIPTOR plus zidovudine and zidovudine monotherapy in 718 HIV-1–infected patients (median age 34.3 years [range 17 to 70 years], 19% female, 32% non-Caucasian).

Patients were treatment naive or had received less than 6 months of prior zidovudine therapy. Mean baseline CD4 cell count was 334 cells/mm^3 (range 75 to 696 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.25 log_{10} copies/mL. Treatment doses were RESCRIPTOR 200 mg, 300 mg, or 400 mg tid plus zidovudine 200 mg tid or zidovudine monotherapy 200 mg tid. No statistically significant difference in CD4 cell count for the combination of RESCRIPTOR plus zidovudine compared with zidovudine monotherapy was observed in a planned analysis at 24 weeks. The mean change from baseline in log_{10} copies/mL plasma HIV-1 RNA is summarized in Fig 1 for RESCRIPTOR 400 mg tid plus zidovudine and zidovudine monotherapy. All patients had not completed 52 weeks at the time of this analysis.

Fig 1: Mean Change From Baseline in Plasma HIV-1 RNA*
Study 0021



*Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

Study 0017 RESCRIPTOR-Didanosine Dual Therapy Trial

Study 0017 was a randomized, double-blind trial comparing treatment with RESCRIPTOR plus didanosine versus didanosine monotherapy in 1,190 HIV-1–infected patients (median age 37.4 years [range 19 to 78 years], 13% female, 32% non-Caucasian). Patients had received up to 4 months prior didanosine therapy; there were no restrictions on prior zidovudine use. Mean baseline CD4 cell count was 142 cells/mm^3 (range 0 to 541 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.77 log_{10} copies/mL. Treatment doses were RESCRIPTOR 400 mg tid plus didanosine or didanosine monotherapy. The dose of didanosine was adjusted by body weight (<60 kg, 125 mg bid; >60 kg, 200 mg bid). Mean changes from baseline in CD4 cell count and log_{10} copies/mL plasma HIV-1 RNA are summarized in Figs 2 and 3, respectively. All patients had not completed 52 weeks at the time of this analysis.

Fig 2: Mean Change From Baseline in CD4 Cell Counts
Study 0017

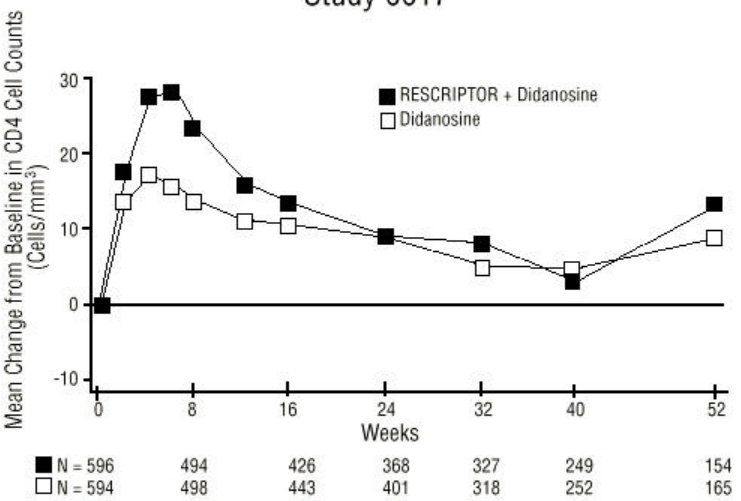
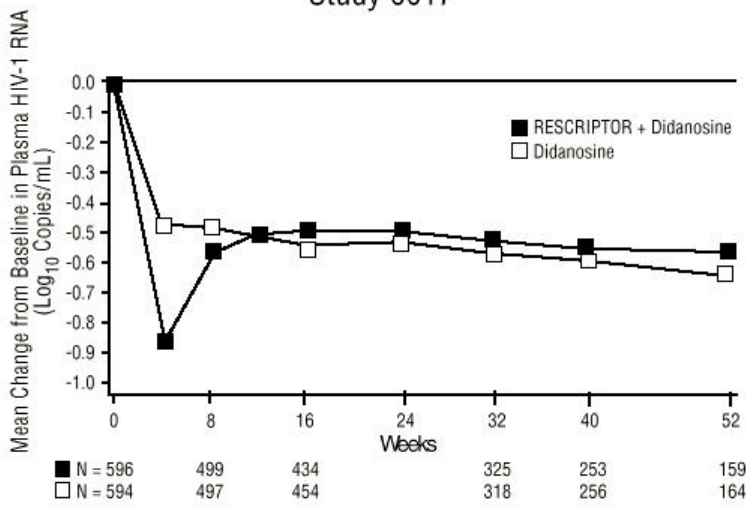


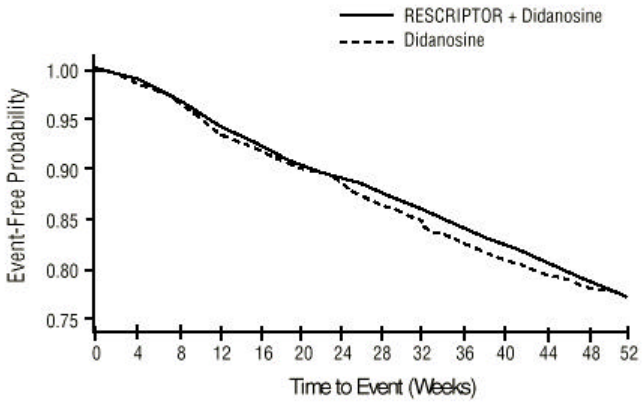
Fig 3: Mean Change From Baseline in Plasma HIV-1 RNA*
Study 0017



* Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

An analysis of clinical efficacy end points (death, clinical progression defined as time to AIDS or death) was performed when all patients had completed at least 6 months in the trial. Comparable rates of deaths and AIDS progression between the didanosine monotherapy arm and the combination of RESCRIPTOR plus didanosine arm were observed. Refer to Fig 4.

Fig 4: Time to Clinical Progression or Death
Study 0017

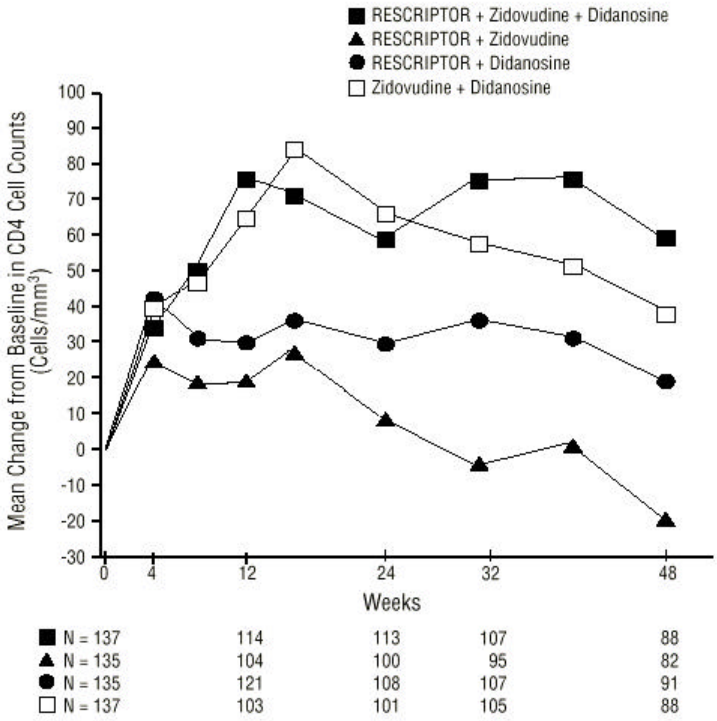


ACTG 261: RESCRIPTOR-Zidovudine-Didanosine Triple Therapy Trial

AIDS Clinical Trials Group (ACTG) Protocol 261 was a randomized trial comparing the following four treatment regimens: RESCRIPTOR plus didanosine, RESCRIPTOR plus zidovudine, RESCRIPTOR plus didanosine and zidovudine, and zidovudine plus didanosine. The study enrolled 544 HIV-1–infected patients (median age 35 years, 18% female and 44% non-Caucasian patients) who were either nucleoside treatment naive or had prior treatment with zidovudine or didanosine (not both) for less than 6 months. Thirty-seven percent reported previous antiretroviral therapy (194 patients with zidovudine and 6 with didanosine). Mean baseline CD4 cell count was 296 cells/mm^3 (range 55 to 640 cells/mm^3). Median baseline plasma HIV-1 RNA level (available for 229 patients) was 4.45 $\log_{10}$ copies/mL (28,260 copies/mL). Treatment doses were RESCRIPTOR 400 mg tid, zidovudine 200 mg tid, and didanosine dose adjusted by body weight (<60 kg, 125 mg bid; >60 kg, 200 mg bid).

Preliminary results showed no statistically significant difference in CD4 cell count for the three drug combination of RESCRIPTOR, zidovudine, and didanosine compared with the combination of zidovudine plus didanosine. No statistically significant difference in plasma HIV-1 RNA for the three-drug combination of RESCRIPTOR, zidovudine, and didanosine compared with the combination of zidovudine plus didanosine was observed. The mean change from baseline in CD4 cell count is shown in Fig 5. The mean change from baseline in plasma HIV-1 RNA is displayed through week 32 due to the small number of subjects having HIV-1 RNA determinations at week 48 and is shown in Fig 6.

Fig 5: Mean Change From Baseline in CD4 Cell Counts
ACTG 261



■ N =	137	114	113	107	88
▲ N =	135	104	100	95	82
● N =	135	121	108	107	91
□ N =	137	103	101	105	88

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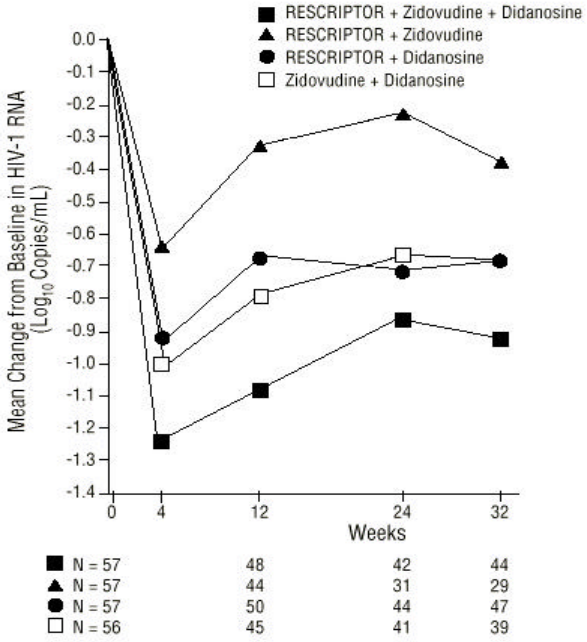
Fig 6: Mean Change From Baseline in
Plasma HIV-1 RNA*, ACTG 261



■ N =	57	48	42	44	
▲ N =	57	44	31	29	
● N =	57	50	44	47	
□ N =	56	45	41	39	

*Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

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CONTRAINDICATIONS

RESCRIPTOR Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulation.

WARNINGS

Coadministration of RESCRIPTOR Tablets with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, calcium channel blockers, ergot alkaloid preparations, amphetamines, cisapride, and sildenafil, may result in potentially serious and/or life-threatening adverse events due to possible effects of RESCRIPTOR on the hepatic metabolism of certain drugs (see PRECAUTIONS section).

PRECAUTIONS

General: Delavirdine is metabolized primarily by the liver. Therefore, caution should be exercised when administering RESCRIPTOR Tablets to patients with impaired hepatic function.

Resistance/Cross-Resistance: Non-nucleoside reverse transcriptase inhibitors, when used alone or in combination, may confer cross-resistance to other non-nucleoside reverse transcriptase inhibitors.

Skin Rash: Skin rash attributable to RESCRIPTOR has occurred in 18% of all patients in combination regimens in phase II and III controlled trials who received RESCRIPTOR 400 mg tid. Forty-two percent to 50% of patients treated with RESCRIPTOR 400 mg tid in Studies 0021 and 0017 experienced rash compared with 24% to 32% of patients receiving monotherapy with zidovudine or didanosine, respectively. In Studies 0021 and 0017, 4.3% of patients treated with RESCRIPTOR 400 mg tid discontinued treatment due to rash.

Dose titration did not significantly reduce the incidence of rash. Rash was typically diffuse, maculopapular, erythematous, and often pruritic. Skin rash was more common in patients with lower CD4 cell counts and usually occurred within 1 to 3 weeks (median = 11 days) of treatment. Rash classified as severe was observed in 3.6% of patients in Studies 0021 and 0017. In most cases, the duration of the rash was less than 2 weeks and did not require dose reduction or discontinuation of RESCRIPTOR. Most patients were able to resume therapy after rechallenge with RESCRIPTOR following a treatment interruption due to rash. The distribution of the rash was mainly on the upper body and proximal arms, with decreasing intensity of the lesions on the neck and face, and progressively less on the rest of the trunk and limbs. Erythema multiforme and Stevens-Johnson syndrome were rarely seen and resolved after withdrawal of RESCRIPTOR. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue RESCRIPTOR and consult a physician. Occurrence of a delavirdine-related rash after 1 month of therapy is uncommon unless prolonged interruption of treatment with RESCRIPTOR occurs. Symptomatic relief has been obtained using diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or topical corticosteroids.

Information for Patients: Patients should be informed that RESCRIPTOR is not a cure for HIV-1 infection and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. Treatment with RESCRIPTOR has not been shown to reduce the incidence or frequency of such illnesses, and patients should be advised to remain under the care of a physician when using RESCRIPTOR.

Patients should be advised that the long-term effects of treatment with RESCRIPTOR are unknown at this time. They should be advised that the use of RESCRIPTOR has not been shown to reduce the risk of transmission of HIV-1.

Patients should be instructed that the major toxicity of RESCRIPTOR is rash and should be advised to promptly notify their physician should rash occur. The majority of rashes associated with RESCRIPTOR occur within 1 to 3 weeks after initiating treatment with RESCRIPTOR. The rash normally resolves in 3 to 14 days and may be treated symptomatically while therapy with RESCRIPTOR is continued. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue medication and consult a physician.

Patients should be informed to take RESCRIPTOR every day as prescribed. Patients should not alter the dose of RESCRIPTOR without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

Patients with achlorhydria should take RESCRIPTOR with an acidic beverage (eg, orange or cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with achlorhydria has not been investigated.

Patients taking both RESCRIPTOR and antacids should be advised to take them at least one hour apart.

Because RESCRIPTOR may interact with certain drugs, patients should be advised to report to their doctor the use of any prescription or over-the-counter medications.

Drug Interactions (see also CLINICAL PHARMACOLOGY-Pharmacokinetics-Drug Interactions)

General: Coadministration of RESCRIPTOR with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, calcium channel blockers, ergot alkaloid preparations, amphetamines, cisapride, and sildenafil, may result in potentially serious and/or life-threatening adverse events. Due to the inhibitory effect of delavirdine on CYP3A and CYP2C9, coadministration of RESCRIPTOR with drugs primarily metabolized by these liver enzymes may result in increased plasma concentrations. Higher plasma concentrations of these drugs could increase or prolong both therapeutic and adverse effects (Table 1). Therefore, appropriate dose adjustments may be necessary for these drugs. Drugs that induce CYP3A may also reduce plasma delavirdine concentrations (Table 2). Physicians should consider using alternatives to drugs that induce CYP3A while a patient is taking RESCRIPTOR.

Table 1. Selected Drugs that are Predicted to Have Plasma Concentrations Increased by Delavirdine *

HIV protease inhibitors: indinavir, saquinavir
Antihistamines: terfenadine,† astemizole†
Antimicrobial agents: clarithromycin, dapsone, rifabutin
Anti-migraine agents: ergot derivatives
Benzodiazepines: alprazolam,† midazolam,† triazolam†
Calcium channel blockers: dihydropyridines, eg, nifedipine
GI motility agents: cisapride†
Other: sildenafil, quinidine, warfarin

* This table is not all inclusive.
† See WARNINGS.

Table 2. Selected Drugs that are Predicted to Decrease Plasma Delavirdine Concentrations ‡ §

Anticonvulsants: carbamazepine, phenobarbital, phenytoin
Antimycobacterial agents: rifabutin, rifampin

‡ This table is not all inclusive.
§ RESCRIPTOR may not be effective when administered concomitantly with these drugs.

Antacids: Doses of an antacid and RESCRIPTOR should be separated by at least one hour, because the absorption of delavirdine is reduced when coadministered with antacids.

Anticonvulsant Agents:

Phenytoin, phenobarbital, carbamazepine: Coadministration of delavirdine with these agents is not recommended, because limited population pharmacokinetic data indicate that a substantial reduction in plasma delavirdine concentrations may result (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Antimycobacterial Agents:

Rifabutin: Coadministration of delavirdine and rifabutin is not recommended, because rifabutin substantially decreases plasma delavirdine concentrations and delavirdine increases plasma concentrations of rifabutin (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Rifampin: Delavirdine should not be coadministered with rifampin, because rifampin reduces delavirdine systemic exposure (AUC) by almost 100% (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Erectile Dysfunction Agents:

Sildenafil: Caution should be used when prescribing sildenafil in patients receiving delavirdine, because delavirdine inhibits CYP3A4 which may result in an increase of sildenafil concentrations. Patients receiving delavirdine and sildenafil should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and prolonged erection, and should report these symptoms

promptly to their physician. Currently, there are no safety and efficacy data available from the use of this combination. If delavirdine and sildenafil are used concomitantly, a single sildenafil dose of 25 mg in a 48-hour period should not be exceeded. This recommendation is based on data from a ritonavir/sildenafil drug-interaction study.

H_2Receptor Antagonists:

Cimetidine, famotidine, nizatidine, and ranitidine: These agents increase gastric pH and may reduce the absorption of delavirdine. Although the effect of these drugs on delavirdine absorption has not been evaluated, chronic use of these drugs with delavirdine is not recommended.

Nucleoside Analogue Reverse Transcriptase Inhibitors:

Didanosine: Administration of didanosine and delavirdine should be separated by at least one hour, because coadministration of didanosine and delavirdine resulted in reduced systemic exposure to both drugs by approximately 20% (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Protease Inhibitors (see CLINICAL PHARMACOLOGY-Pharmacokinetics)**:**

Amprenavir: Delavirdine has the potential to increase serum concentrations of amprenavir.

Indinavir: Due to an increase in indinavir plasma concentrations (preliminary results), a dose reduction of indinavir to 600 mg tid should be considered when delavirdine and indinavir are coadministered. Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir: No studies have been conducted with combination therapy of delavirdine and ritonavir at their recommended doses. Preliminary results indicate there is no evidence of an interaction at doses of delavirdine 400 mg to 600 mg bid and ritonavir 300 mg bid. Currently, there are no safety and efficacy data available from the use of this combination.

Saquinavir: Saquinavir AUC increased 5-fold when delavirdine (400 mg tid) and saquinavir (600 mg tid) were administered in combination. Currently, there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13% of subjects during the first several weeks of the delavirdine and saquinavir combination (6% grade 3 or 4). Hepatocellular enzymes (ALT/AST) should be monitored frequently if this combination is prescribed.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term carcinogenicity studies with delavirdine in animals have not been completed. A battery of genetic toxicology tests was conducted with delavirdine, including the Ames assay, in vitro unscheduled DNA synthesis (UDS) assay, an in vitro cytogenetics (chromosome aberration) assay in human peripheral lymphocytes, a mammalian mutation assay in Chinese hamster ovary cells, and the micronucleus test in mice. The results were negative indicating delavirdine is not mutagenic.

Delavirdine at doses of 20, 100, and 200 mg/kg/day did not cause impairment of fertility in rats when males were treated for 70 days and females were treated for 14 days prior to mating.

Pregnancy: Pregnancy Category C: Delavirdine has been shown to be teratogenic in rats. Delavirdine caused ventricular septal defects in rats at doses of 50, 100, and 200 mg/kg/day when administered during the period of organogenesis. The lowest dose of

delavirdine that caused malformations produced systemic exposures in pregnant rats equal to or lower than the expected human exposure to RESCRIPTOR (C_{min}≈15 μM) at the recommended dose. Exposure in rats approximately 5-fold higher than the expected human exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival. Additionally, reduced pup survival on postpartum day 0 occurred at an exposure (mean C_{min}) approximately equal to the expected human exposure. Delavirdine was excreted in the milk of lactating rats at a concentration three to five times that of rat plasma.

Delavirdine at doses of 200 and 400 mg/kg/day administered during the period of organogenesis caused maternal toxicity, embryotoxicity and abortions in rabbits. The lowest dose of delavirdine that resulted in these toxic effects produced systemic exposures in pregnant rabbits approximately 6-fold higher than the expected human exposure to RESCRIPTOR (C_{min}≈15 μM) at the recommended dose. The no-observed-adverse-effect dose in the pregnant rabbit was 100 mg/kg/day. Various malformations were observed at this dose, but the incidence of such malformations was not statistically significantly different from those observed in the control group. Systemic exposures in pregnant rabbits at a dose of 100 mg/kg/day were lower than those expected in humans at the recommended clinical dose. Malformations were not apparent at 200 and 400 mg/kg/day; however, only a limited number of fetuses were available for examination as a result of maternal and embryo death.

No adequate and well-controlled studies in pregnant women have been conducted. RESCRIPTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of 7 unplanned pregnancies reported in premarketing clinical studies, 3 were ectopic pregnancies and 3 pregnancies resulted in healthy live births. One infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately six weeks of treatment with delavirdine and zidovudine early in the course of the pregnancy.

Nursing Mothers: The U.S. Public Health Services Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Pediatric Use: Safety and effectiveness of delavirdine in combination with other antiretroviral agents have not been established in HIV-1–infected individuals younger than 16 years of age.

ADVERSE REACTIONS

The safety of RESCRIPTOR Tablets alone and in combination with other therapies has been studied in 1,969 patients receiving RESCRIPTOR.

Adverse events of moderate or severe intensity reported in ≥ 2% of patients receiving RESCRIPTOR in combination with didanosine or zidovudine in Studies 0017 and 0021 are summarized in Table 3. The median duration of treatment in Studies 0017 and 0021 was 34 and 42 weeks (up to 107 weeks for both studies), respectively, at the time of the safety assessment. The most frequently reported drug-related medical event was rash (see PRECAUTIONS-Skin Rash).

Table 3. , Adverse Events of Moderate or Severe Intensity in ≥2% of Patients Receiving RESCRIPTOR*

Body System/ Adverse Event	Study 0017		Study 0021	
	Didanosine† 200 mg bid (n=591)	Delavirdine 400 mg tid + Didanosine† 200 mg bid (n=594)	Zidovudine 200 mg tid (n=271)	Delavirdine 400 mg tid + Zidovudine 200 mg tid (n=287)
Body as a Whole				
Headache	4.7	5.6	4.8	5.6
Fatigue	2.7	2.9	4.8	5.2
Digestive				
Nausea	3.4	4.9	6.6	10.8
Diarrhea	4.4	4.5	2.2	3.5
Vomiting	1.2	2.4	1.1	2.8
Metabolic and Nutritional				
Increased ALT (SGPT)	3.6	5.2	0.7	2.4
Increased AST (SGOT)	3.0	4.5	0.7	1.7
Skin				
Rash	3.0	9.8	1.5	12.5
Maculopapular rash	2.0	6.6	1.1	4.5
Pruritus	1.7	2.2	1.5	3.1

* Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.
† Dose adjusted body weight < 60 kg = 125 mg bid; ≥ 60 kg = 200 mg bid.

Medical events occurring in less than 2% of patients receiving RESCRIPTOR (in combination treatment) in all phase II and III studies, considered possibly related to treatment, and of at least ACTG grade 2 in intensity are listed below by body system.
Body as a Whole: Abdominal cramps, abdominal distention, abdominal pain (generalized or localized), allergic reaction, asthenia, back pain, chest pain, chills, edema (generalized or localized), epidermal cyst, fever, flank pain, flu syndrome, lethargy, lip edema, malaise, neck rigidity, pain (generalized or localized), sebaceous cyst, trauma, and upper respiratory infection.
Cardiovascular System: Bradycardia, migraine, pallor, palpitation, postural hypotension, syncope, tachycardia, and vasodilation.
Digestive System: Anorexia, aphthous stomatitis, bloody stool, colitis, constipation, decreased appetite, diarrhea (Clostridium difficile), diverticulitis, duodenitis, dry mouth, dyspepsia, dysphagia, enteritis, esophagitis, fecal incontinence, flatulence, gagging, gastritis, gastroesophageal reflux, gastrointestinal bleeding, gastrointestinal disorder, gingivitis, gum hemorrhage, increased appetite, increased saliva, increased thirst, mouth ulcer, nonspecific hepatitis, pancreatitis, rectal disorder, sialadenitis, stomatitis, and tongue edema or ulceration.
Hemic and Lymphatic System: Anemia, bruise, ecchymosis, eosinophilia, granulocytosis, neutropenia, pancytopenia, petechia, prolonged partial thromboplastin time, purpura, spleen disorder, and thrombocytopenia.
Metabolic and Nutritional Disorders: Alcohol intolerance, bilirubinemia, hyperkalemia, hyperuricemia, hypocalcemia, hyponatremia, hypophosphatemia, increased gamma glutamyl transpeptidase, increased lipase, increased serum alkaline phosphatase, increased

serum amylase, increased serum creatine phosphokinase, increased serum creatinine, peripheral edema, and weight increase or decrease.

Musculoskeletal System: Arthralgia or arthritis of single and multiple joints, bone disorder, bone pain, leg cramps, muscular weakness, myalgia, tendon disorder, tenosynovitis, and tetany.

Nervous System: Abnormal coordination, agitation, amnesia, anxiety, change in dreams, cognitive impairment, confusion, decreased libido, depressive symptoms, disorientation, dizziness, emotional lability, hallucination, hyperesthesia, hyperreflexia, hypesthesia, impaired concentration, insomnia, manic symptoms, muscle cramp, nervousness, neuropathy, nightmares, nystagmus, paralysis, paranoid symptoms, paresthesia, restlessness, somnolence, tingling, tremor, vertigo, and weakness.

Respiratory System: Bronchitis, chest congestion, cough, dyspnea, epistaxis, laryngismus, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages: Angioedema, dermal leukocytoclastic vasculitis, dermatitis, desquamation, diaphoresis, dry skin, erythema, erythema multiforme, folliculitis, fungal dermatitis, hair loss, nail disorder, petechial rash, seborrhea, skin disorder, skin nodule, Stevens-Johnson syndrome, urticaria, and vesiculobullous rash.

Special Senses: Blepharitis, conjunctivitis, diplopia, dry eyes, ear pain, photophobia, taste perversion, and tinnitus.

Urogenital System: Breast enlargement, calculi of the kidney, epididymitis, hematuria, hemospermia, impotence, kidney pain, metrorrhagia, nocturia, polyuria, proteinuria, and vaginal moniliasis.

Laboratory Abnormalities: The frequency of clinically important laboratory abnormalities observed during therapy in Studies 0017 and 0021 is summarized in Table 4. There was no significant difference in ACTG grades 3 and 4 laboratory abnormalities between treatment groups except a two-fold reduction in neutropenia in the delavirdine plus zidovudine combination group compared with the zidovudine monotherapy group in Study 0021.

Table 4. , Frequency (%)* of Clinically Important Laboratory Abnormalities

Laboratory Test	Study 0017		Study 0021	
	Didanosine† (n=591)	Delavirdine 400 mg tid + Didanosine† (n=594)	Zidovudine 200 mg tid (n=271)	Delavirdine 400 mg tid + Zidovudine 200 mg tid (n=287)
Neutropenia (ANC <750/mm³)	6.7	5.7	7.7‡	3.5
Anemia (Hgb <7.0 g/dL)	0.2	0.7	1.1	1.0
Thrombocytopenia (platelets <50,000/mm³)	1.4	1.5	0.0	0.0
ALT (>5.0 x ULN)	4.6	6.7	3.7	3.8
AST (>5.0 x ULN)	4.9	5.6	3.0	2.1
Bilirubin (>2.5 ULN)	0.7	0.5	0.4	1.0
Amylase (>2.0 ULN)	6.5	5.2	1.1	0.0

* Percentage was based on the number of patients for which data on that laboratory test was available.
† Dose adjusted by body weight <60 kg = 125 mg bid; ≥ 60 kg = 200 mg bid.
‡ Significant (*P*<.05) delavirdine + zidovudine vs zidovudine.
ANC = Absolute neutrophil count; ULN = upper limit of normal.

OVERDOSAGE

No reports of overdose with RESCRIPTOR Tablets are available in humans. Several patients have received up to 850 mg tid for up to 6 months with no serious drug-related medical events.

Management of Overdosage: Treatment of overdosage with RESCRIPTOR should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. There is no specific antidote for overdosage with RESCRIPTOR. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Since delavirdine is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to result in significant removal of the drug.

DOSAGE AND ADMINISTRATION

The recommended dosage for RESCRIPTOR Tablets is 400 mg (four 100-mg or two 200-mg tablets) three times daily. RESCRIPTOR should be used in combination with other appropriate antiretroviral therapy. The complete prescribing information for other antiretroviral agents should be consulted for information on dosage and administration.

The 100-mg RESCRIPTOR Tablets may be dispersed in water prior to consumption. To prepare a dispersion, add four 100-mg RESCRIPTOR Tablets to at least 3 ounces of water, allow to stand for a few minutes, and then stir until a uniform dispersion occurs (see CLINICAL PHARMACOLOGY-Pharmacokinetics-Absorption and Bioavailability). The dispersion should be consumed promptly. The glass should be rinsed with water and the rinse swallowed to insure the entire dose is consumed. **The 200-mg tablets should be taken as intact tablets, because they are not readily dispersed in water.** Note: The 200-mg tablets are approximately one third smaller in size than the 100-mg tablets.

RESCRIPTOR Tablets may be administered with or without food (see CLINICAL PHARMACOLOGY- Pharmacokinetics-Absorption and Bioavailability). Patients with achlorhydria should take RESCRIPTOR with an acidic beverage (eg, orange or cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with achlorhydria has not been investigated.

Patients taking both RESCRIPTOR and antacids should be advised to take them at least one hour apart.

HOW SUPPLIED

RESCRIPTOR Tablets are available as follows:

100 mg: white, capsule-shaped tablets marked with “U 3761”.
Bottles of 360 tablets NDC 0009-3761-03

200 mg: white, capsule-shaped tablets marked with “RESCRIPTOR 200 mg”.
Bottles of 180 tablets NDC 0009-XXXX-XX

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Keep container tightly closed. Protect from high humidity

Rx only

ANIMAL TOXICOLOGY

Toxicities among various organs and organ systems in rats, mice, rabbits, dogs, and monkeys were observed following the administration of delavirdine. Necrotizing vasculitis was the most significant toxicity that occurred in dogs when mean nadir serum concentrations of delavirdine were at least 7-fold higher than the expected human exposure to RESCRIPTOR (C_{min}≈15 μM) at the recommended dose. Vasculitis in dogs was not reversible during a 2.5-month recovery period; however, partial resolution of the vascular lesion characterized by reduced inflammation, diminished necrosis, and intimal thickening occurred during this period. Other major target organs included the gastrointestinal tract, endocrine organs, liver, kidneys, bone marrow, lymphoid tissue, lung, and reproductive organs.

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Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA

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